Ursodeoxycholic acid

Ursodiol (ursodeoxycholic acid; UDCA; URSO; Actigall) is a bile acid originally identified in black bears; the name ursodiol derives from the Latin name of the bear family, Ursidae. It was first used in Western medicine for the dissolution of gallstones in gall bladder disease patients. Both primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) cause accumulation of toxic bile acids (such as deoxycholic acid (DCA)) in the liver, leading to cell death. The beneficial effects of ursodiol in PBC and PSC patients are in part attributable to a protective effect of this bile acid against toxic bile acids in liver cells. In addition, ursodiol increases bile transport activity, stimulating hepatobiliary secretion by preserving activity of the bile-salt export pump (BSEP), a key component of the bile transport system in the liver.

UDCA also seems to have anti-inflammatory properties. It binds to the glucocorticoid receptor and suppresses a key inflammatory component, nuclear factor-kappaB. Anticholestatic effects of ursodiol have also been reported in other liver diseases, including progressive familial intrahepatic cholestasis, intrahepatic cholestasis of pregnancy, and liver disease associated with cystic fibrosis.

In the U.S.A., ursodiol is available under two trade names; Actigall (typically available as 300 mg gelatin capsules with a pink cap and white body containing a white/yellowish powder), and URSO (typically available as white 250 mg tablets) [URSO 250]. Actigall was developed by Novartis Pharmaceuticals Corporation and is now marketed by Watson Pharmaceuticals:

http://www.watsonpharm.com/

The Actigall capsules also contain as inactive ingredients: colloidal silicon dioxide, ferric oxide, gelatin, magnesium stearate, starch (corn), and titanium dioxide.

URSO is marketed by Axcan Pharma:

http://www.axcan.com/

Axcan Pharma has recently developed a 500 mg tablet marketed as URSO Forte. The inactive ingredients of URSO are: microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, ethylcellulose, dibutyl sebacate, carnauba wax, hydroxypropyl methylcellulose, PEG 3350, PEG 8000, cetly alcohol, sodium lauryl sulfate, and hydrogen peroxide. According to researchers at Mayo clinic “Milligram per milligram, the bioavailability of Actigall preparation is about two-thirds that of the URSO 250 tablet available in the United States”. According to Axcan Pharma “URSO Forte and URSO 250 are the only ursodiol approved by the Food and Drug Administration for the treatment of patients with PBC.

In Australia, ursodiol is available as Ursofalk (Dr Falk Pharma GmbH) as white, opaque, hard gelatin capsules. Each Ursofalk capsule contains 250 mg of ursodeoxycholic acid. These capsules also contain maize starch, silicon dioxide, magnesium stearate, gelatin and titanium dioxide as inactive ingredients. A liquid formulation of Ursofalk has been developed for pediatric patients.

The recommended adult dosage for URSO Forte and URSO 250 in the treatment of PBC is 13-15 mg/kg/day administered in two to four divided doses with food. Evidence is accumulating that ursodiol is more effective in delaying PBC progression when provided in early stages of the disease (stages 1 to 2), and shows little effect in late stage disease (stage 4).

URSO is marketed by Axcan Pharma:

http://www.axcan.com/

Cholestyramine

Cholestyramine (Questran) is a bile-sequestering resin that absorbs bile and cholesterol in the gut, and is then excreted in the faeces. This material is not absorbed into the blood stream, and remains in the gut. It is essential that when ursodiol is also prescribed, cholestyramine should not be taken at the same time, as this will prevent ursodiol uptake in the gut. The two medications are usually staggered approx. 4 hours apart. Patients describe taking cholestyramine as like “drinking liquid sand”.

Rifampin

Rifampin (rifampicin) is an antibiotic mostly used for the treatment of tuberculosis. However, it has an important secondary effect of activating a nuclear receptor (transcription factor) in the gut and liver, called the pregnane X receptor (PXR). PXR (also known as the steroid and xenobiotic receptor, SXR) controls the expression of a number of enzymes of bile acid and xenobiotic detoxification, and bile transport proteins. It is thought that these actions facilitate more efficient excretion and metabolism of bile acids in cholestasis, alleviating pruritus. It has been proposed that ursodiol and rifampin may be complementary in their actions. Activation of PXR may have other beneficial effects, including inhibition of inflammation by suppression of nuclear factor-kappa B, and inhibition of fibrosis. However, rifampin may cause increased metabolism of a number of drugs, and it may be necessary to adjust the dose of these other medications when supplied with rifampin. Your doctor will advise you about contraindications and medication dose adjustments.
Primary sclerosing cholangitis (PSC) is a cholestatic liver disease, meaning that bile flow from the liver to the small bowel is slow or static. Accumulation of toxic bile acids in the liver can result in damage to liver cells, and increase potential for cancer development in the bile ducts and colon. Medications used for PSC include the bile acid urso-deoxycholic acid (UDCA). UDCA stimulates bile flow and protects liver cells against toxic bile acids, thereby improving liver biochemistry. However it is unclear at present whether this therapy significantly delays disease progression and leads to increased survival free of liver transplantation. Pruritus (itching) is often treated with bile-sequestering agents, such as cholestyramine, or compounds that stimulate bile acid transport and metabolism, such as rifampin. Medications used for control of inflammatory bowel disease (IBD) associated with PSC will be considered in a separate brochure.

Where Can I Find Support and Information?

PSC Partners Seeking a Cure is a 501(c)3 nonprofit foundation that endeavors to find a cure for Primary Sclerosing Cholangitis. Please consider joining our mailing list at:

www.pscpartners.org

This foundation offers an annual conference for PSC patients and caregivers, and publishes a quarterly newsletter. Many members of this organization are also members of an on-line PSC support group:

http://health.groups.yahoo.com/group/psc-support/

A comprehensive list of www resources and scientific literature on PSC and IBD, and allied autoimmune diseases can be found at:

www.psc-literature.org

For detailed information on inflammatory bowel disease please visit the Crohn's And Colitis Foundation of America (CCFA) web site at:

www.ccfa.org

Primary Sclerosing Cholangitis: Medications

Antibiotics

Oral Vancomycin

Recent studies at Stanford University indicate that many pediatric patients with PSC show marked improvements in liver biochemistry (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT)) when treated with oral vancomycin. Further research is needed to determine whether a similar protocol will be of therapeutic benefit in the adult population.

Ciprofloxacin

One of the major challenges in PSC is the occurrence of bacterial cholangitis; a bacterial infection of the biliary tree. Such infections are often associated with chills and fever, right upper-quadrant pain, dark urine, pale stools, nausea and vomiting. If left untreated these biliary infections can rapidly progress to sepsis and death. Antibiotics used to treat these infections include Ciprofloxacin (Cipro).

ABC Regimen

Repeated cholangitis attacks are sometimes managed by a rotating antibiotic regimen often termed “ABC”, in which patients take Augmentin, Bactrim DS, and Cipro alternately to minimize development of bacterial antibiotic resistance.

Other

Endoscopic procedures such as ERCP can potentially introduce bacteria into the bile ducts. Many centers prescribe antibiotics for patients undergoing ERCP to prevent this complication. However, there are conflicting results concerning the efficacy of such prophylactic antibiotics in prevention of post-ERCP pancreatitis.

Corticosteroids

Corticosteroids, and other immunosuppressants, have been found to be ineffective in favorably altering the course of classic PSC. However, it should be emphasized that there may be sub-groups of patients who may show excellent response to corticosteroids. Thus, it is essential to identify these patients as early as possible in the disease course. These patients include those with autoimmune hepatitis (AIH)/primary sclerosing cholangitis (PSC) overlap syndrome, and patients with IgG4 sclerosing cholangitis resembling autoimmune pancreatitis (AIP). In the IgG4 sub-type of sclerosing cholangitis, as in AIP, serum IgG4 is markedly elevated. The latter group is estimated to comprise about 7-10% of patients with PSC. The AIH/PSC overlap syndrome tends to be more common in children.

Adverse Effects

Medications are rarely free of side-effects; some side-effects may be mild, others severe. When prescribed any medication, you should read the drug safety sheet provided and become familiar with all potential adverse effects of the medication. Consult your doctor immediately if you experience any of the symptoms described in the drug safety sheet(s).